Remarks

I. Status of the Claims

Claims 1-15 are pending in the current patent application.

Claims 1 and 11 have been amended by changing the phrase "comprising" to "consisting of."

II. Claims 1-15 are Non-obvious over the combination of US 6,448,225 and US 5,358,708 and Cleland

Claims 1-15 stand rejected under 35 USC 103(a) as being allegedly obvious over the combination of O'Conner et al., US 6,448,225 (the '225 patent) in view of Patel,S, US 5,358,708 (the '708 patent) and further in view of Cleland et al., Pharmaceutical Research , Vol. 13, No. 10, 1996 (Cleland). Applicants respectfully traverse the rejection of claims 1-15.

The Examiner has alleged that one skilled in the art would have found the claimed formulation of hGH, along with methionine and polyethylene glycol to be prima facie obvious because the '225 patent teaches hGH formulations with a buffer, nonionic surfactant, polyethylene polymer, tonicity agent and preservative, the '708 patent teaches formulations that use methionine and Cleland teach formulations of hGH that are formulated with polyethylene glycol. Applicants respectfully submit that the instantly claimed formulation of hGH which also requires methionine and polyethylene glycol is non-obvious in view of the combination of '225, '708 and Cleland.

The Supreme Court held in *KSR Int'l Co. v Teleflex Inc.,* 127 S.Ct.1727 (2007), that the proper test of obviousness under its precedent is an application of the *Graham* factors, not a rigid application of the teaching, suggestion, motivation (TSM) test. Under *Graham*, the factors are: (1) the scope and content of the prior art; (2) the differences between the prior art and claims at issue; (3) the level of ordinary skill in the art; and (4) secondary conditions evidencing non-obviousness. In its analysis, the Court however emphasized that although a precise teaching, suggestion or motivation in the prior art is not required, "it [is] important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements in a way the claimed new invention does." "[R}ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support a legal conclusion of obviousness." *KSR* at 1741.

The Supreme Court stated that there is no inconsistency between the idea underlying the TSM test and the *Graham* analysis and that the Federal Circuit had applied the test properly

in many cases. *KSR*, 127 S. Ct. at 1741. The Supreme Court also noted in *KSR* that the Federal Circuit had expressed that its TSM test was flexible, citing *Dystar v. C.H. Patrick*, 464 F.3d 1356-1367 (2006). *KSR* 127 S. Ct. at 1743.

It is that flexible TSM test that the Federal Circuit has relied upon in post-*KSR* obviousness cases.

In *Omegaflex v. Parker-Hannifin Corporation*, 243 Fed. Appx. 592 (decided on June 18, 2007), Judge Michel careful to follow citations to *KSR* with citations to Federal Circuit decisions stated "[W]e have stated explicitly that evidence of a motivation to combine need not be found in the prior art themselves."

In *Cordis Corporation v. Medtronic Ave. Inc.*, 511 F.3d 1157 (decided on January 7, 2008), one issue on appeal was a challenge to a jury instruction on obviousness. The instruction at issue was:

> "If the prior art references as a whole do not teach, suggest or motivate that combination, then they may not be combined. The mere fact that the prior art can be modified does not make the modification obvious unless the prior art suggests the desirability of the modification." "A suggestion to combine references may also flow from the nature of the problem or from the ordinary knowledge of those skilled in the art that certain references are of special importance."

In upholding the instruction as proper, Judge Bryson rebuffed the argument that *KSR* resulted in a significant change in the law to warrant a new trial. The court noted that *KSR* made clear that the TSM test cannot be rigidly applied so as to limit the obviousness inquiry. Judge Bryson noted that the Supreme Court stated there is no inconsistency between the idea underlying the TSM test and the *Graham* factors and that the TSM test can provide helpful insight to an obviousness inquiry. *Cordis*, 511 F.3d at 1172.

Judge Rader noted that the Federal Circuit's flexible TSM test remains the primary guarantor against hindsight in *Ortho-McNeil Pharmaceutical, Inc v. Mylan Laboratories, Inc.*, 2008 WL 834402 (Fed. Cir. (NJ)) (decided March 31 2008). In *Innogenetics, N.V. v. Abbott Laboratories*, 512 F.3d 1363 (decided January 17, 2008) Judge Moore observed that while the Supreme Court made it clear in *KSR* that the TSM test cannot be a rigid rule that limits the obviousness inquiry, also noted that "We must be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be considered to produce the claimed invention."

The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed

invention. *Alza Corp. v. Mylan Laboratories Inc.*, 391 F.3d 1365, 1372-1373 (Fed. Cir. 2004). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. *In re Napier*, 55 F.3d 610, 613, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995).

The Examiner has admitted that the '225 patent does not teach aqueous formulations of human growth hormone that comprise methionine or polyethylene glycol. The Examiner then states that modification of '225 with the combination of the teachings of the '708 patent and Cleland renders the instantly claimed invention obvious.

The lack of teaching of a formulation comprising hGH, methionine and polyethylene glycol is not cured by combining the '225 patent with the '708 patent and Cleland. The '708 patent teaches formulations of an interferon, granulocyte-macrophage colony stimulating factor or an interleukin in a buffer with methionine or histidine. There is no mention of a formulation comprising hGH in the '708 reference and also no reference of a formulation comprising polyethylene glycol. In addition, there is no suggestion in '708 that use of methionine would be successful in stabilizing an entirely different protein such as hGH. In fact, the '708 recognized that there is considerable uncertainty in arriving at stabilized formulations of proteins. The '708 patent clearly recognized that different formulations of the proteins interferon, granulocyte-macrophage colony stimulating factor or an interleukin behave differently depending on the nature of the protein itself. At column 4, line 14-18 of '708 it states that "Also, the storage prolonging effects of methionine and histidine are not equivalent with the different proteins and, of course, mixtures of the amino acids will exhibit different effects as the ratio is varied, the identity of the protein is changed and/or the concentrations are altered." Applicants submit that this passage clearly shows that the '708 inventors recognized that there is uncertainty in obtaining a stabilized formulation of a protein based on the nature and identity of the specific protein employed. The '708 patent does not equate all proteins and does not mention nor suggest in any way that hGH could be stabilized by addition of methionine or histidine. One of ordinary skill in the art, in view of '708, would not know whether or not methionine would work to stabilize an aqueous formulation of hGH as instantly claimed. A conclusion that methionine would stabilize an aqueous hGH formulation based on the teachings of '708 could only be based on speculation.

The Examiner has then relied on Cleland for the teaching that hGH is formulated with polyethylene glycol to provide stability and improved yield. Applicants respectfully submit that Cleland teaches various formulations of hGH that are buffered at pH 8 in sodium phosphate and are aqueous emulsions in the organic solvents ethyl acetate or methylene chloride. The

formulations of Cleland are in organic solvents and as such are used for encapsulation into microspheres. The formulations of Cleland differ from the instant formulation in that the pH is higher and Cleland provides aqueous/organic emulsions in which either ethyl acetate or methylene chloride is necessarily present.

Beyond looking to the prior art to determine if it suggests doing what the inventor has done, one must also consider if the art provides the required expectation of succeeding in that endeavor. *See In re Dow Chem. Co.*, 837 F.2d at 473, 5 U.S.P.Q.2d at 1531. "Obviousness does not require *absolute* predictability, but a reasonable expectation of success is necessary." *In re Clinton*, 527 F.2d 1226, 1228, 188 U.S.P.Q. 365, 367 (C.C.P.A. 1976).

Applicants also submit that one of ordinary skill in the art would not be motivated to modify the combination of O'Conner, Patel and Cleland to arrive at the instantly claimed invention since there is no motivation to do so. The obviousness rejection is based on combination of Patel et. al., which references the use of methionine as a stabilizer without the use of a polymer stabilizer for the following proteins: interleukin, interferon, and granulocyte macrophage colony stimulating factor with the O'Conner hGH formulation which lacks both the polymer stabilizer and methionine. Cleland provides an emulsified aqueous/organic formulation of hGH used for encapsulation into microspheres which requires the presence of an organic solvent (ethyl acetate or methylene chloride) and wherein the aqueous sodium phosphate buffer is at pH 8, which is at a higher pH than the instantly claimed formulation, and which may or may not contain polyethylene glycol to stabilize the hGH from being denatured by the organic solvent.

One of ordinary skill in the art would not be motivated to modify the combination of O'Conner, Patel and Cleland since the use of methionine as a stabilizer is not only protein specific, but can also be pH specific and is therefore methionine is not known as a common stabilizer. The literature also discloses that the use of methionine as a stabilizer is very dependent upon the protein and the conditions of the formulation. In fact, even the use of methionine in formulating granulocyte macrophage colony stimulating factor referenced in Patel et. al., has been shown to only be a stabilizer at acidic conditions and have no effect when formulating at alkaline conditions (see J. Yin, J Chu, M.S Ricci, D. Brems, D Wang, and B. Trout. Effects of Antioxidants on the Hydrogen Peroxide Mediated oxidation of Methionine Residues in Granulocyte Colony Stimulating Facto and Human Parathyroid Hormone Fragment 13-34. *Pharmaceutical Research.* Vol. 21, No. 12, December 2004, IDS filed in previous response). Cleland would have to be substantially modified since the hGH formulations described therein require the presence of an organic solvent and the pH of the buffer would need to be lowered.

Example 6 provided in the instant patent application shows the advantageous stability profile of the formulation of hGH with methionine and a polyethylene glycol polymer stabilizer as instantly claimed. Applicants respectfully submit that the improved stability profile provides a formulation of hGH that is not suggested by the cited references. For these reasons, Applicants respectfully request the Examiner to reconsider claims 1-15 and withdraw the 35 USC § 103(a) rejection.

In view of the foregoing remarks, applicants respectfully request that this rejection of claims 1-15 be withdrawn.

Based on the amendments to the Claims and the arguments provided above, Applicants respectfully submit that Claims 1-15 are in condition for allowance.

Respectfully Submitted:

Date: 9 December 2010

/ John A. Wichtowski /
John A. Wichtowski
Attorney for Applicants
Registration No. 48,032

Pfizer Inc.
Patent Department, MS-9114
Eastern Point Road
Groton, Connecticut 06340
(860) 715-6645